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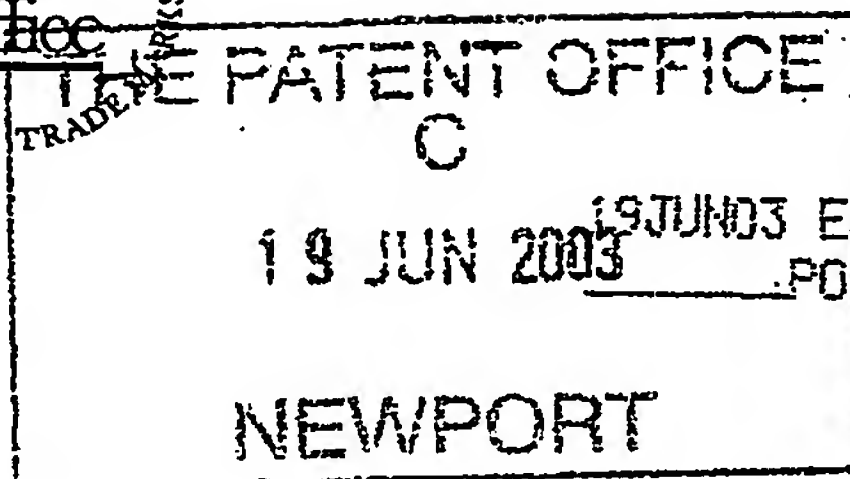
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Patents Form 1/77

Patents Act 1977
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101119-1 GB

2. Patent application number
(The Patent Office will fill in this part)

19 JUN 2003

0314261.9

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number (If you know it)

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent (if you have one)

Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number (if you know it)

7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form

Description 21

Claim(s) 4

Abstract 1

Drawing(s)

21

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

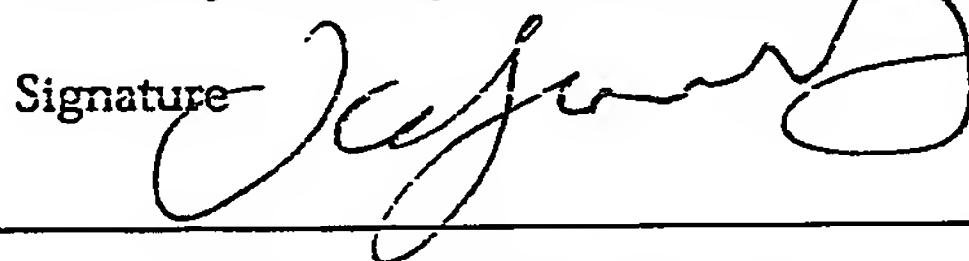
Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature



Date 18/06/03

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer Bennett - 01625 230148

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Therapeutic AgentsField of invention

- 5 The present invention relates to certain pyrazine compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

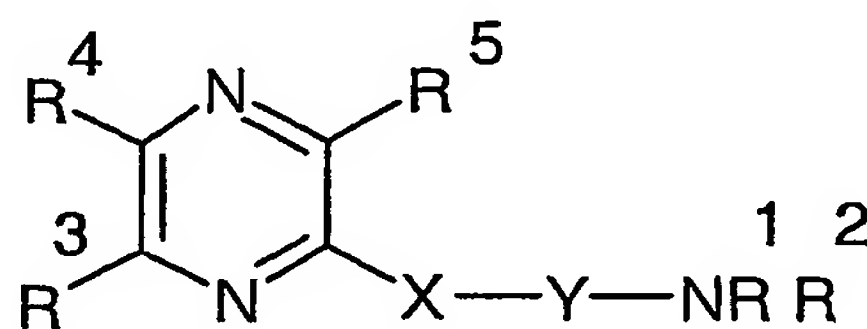
10 Background of the invention

It is known that certain CB₁ modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB₁ modulators with improved physicochemical
15 properties and/or DMPK properties and/or pharmacodynamic properties.

Pyrazinecarboxamides are reported to possess antithrombotic properties (WO 92/ 02513). The compounds disclosed in this document are disclaimed from the compound claims of the present invention. 5,6-Diphenyl-2-pyrazinecarboxylic acid is disclosed in CH 458 361.

20

Co-pending application PCT/GB02/05742 discloses compounds of the general formula (A)



A

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in
25 which

R¹ and R² independently represent :

a C₁₋₆alkyl group;

an (amino)C₁₋₄alkyl- group in which the amino is optionally substituted by one or more C₁₋₃alkyl groups;

an optionally substituted non-aromatic C₃₋₁₅carbocyclic group;

a (C₃₋₁₂cycloalkyl)C₁₋₃alkyl- group;

a group $-(CH_2)_r(phenyl)_s$ in which r is 0, 1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2

and the phenyl groups are optionally independently substituted by one, two or three groups

5 represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is

10 optionally substituted by one or more C₁₋₃alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group $-(CH_2)_t Het$ in which t is 0, 1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C₁₋₃alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C₁₋₅alkyl group, a C₁₋

15 alkoxy group or halo;

or R¹ represents H and R² is as defined above;

or R¹ and R² together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is

20 optionally substituted by one or more C₁₋₃alkyl groups, hydroxy or benzyl ;

X is CO or SO₂;

Y is absent or represents NH optionally substituted by a C₁₋₃alkyl group;

R³ and R⁴ independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

25

Z represents a C₁₋₃alkyl group, a C₁₋₃alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C₁₋₃alkylamino, mono or di C₁₋₃alkylamido, C₁₋₃alkylsulphonyl, C₁₋₃alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C₁₋₃alkyl carbamoyl, sulphamoyl and acetyl; and

30

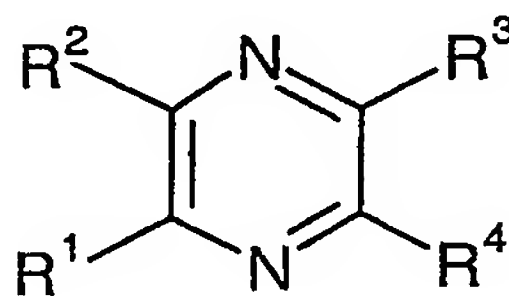
R⁵ is H, a C₁₋₃alkyl group, a C₁₋₃alkoxymethyl group, trifluoromethyl, a hydroxyC₁₋₃alkyl group, C₁₋₃alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C₁₋₃alkylcarbamoyl,

acetyl, or hydrazinocarbonyl of formula $-\text{CONHN}^a\text{R}^b$ wherein R^a and R^b are as previously defined for R^1 and R^2 respectively;

with the proviso that when R^1 and R^2 together with the nitrogen atom to which they are attached represent 4-methylpiperazin-1-yl or R^1 represents H and R^2 represents methyl or 1-benzylpiperidin-4-yl; X is CO; Y is absent and R^5 is H; then R^3 and R^4 do not both represent 4-methoxyphenyl; and their use in the treatment of obesity, psychiatric and neurological disorders.

10 Description of the invention

The invention relates to a compound of formula (I)



I

15 and pharmaceutically acceptable salts thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is independently optionally substituted by one or more groups represented by Z;

Z represents a C_{1-8} alkyl group, a C_{1-6} alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, mono or di C_{1-3} alkylamido, C_{1-3} alkylsulphonyl, C_{1-3} alkylsulphonyloxy, C_{1-3} alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3} alkyl carbamoyl, sulphamoyl, acetyl, an aromatic heterocyclic group which is optionally substituted by one or more halo, C_{1-4} alkyl, trifluoromethyl or trifluoromethoxy and a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, hydroxy, fluoro, benzyl or an amino group $-\text{NR}^x\text{R}^y$ in which R^x and R^y independently represent H or C_{1-4} alkyl

;

R^3 and R^4 independently represent a group of formula $(CH_2)_nCOOR^7$

in which n is 0, 1, 2, 3 or 4; and R^7 represents a C_{1-12} alkyl group, a C_{3-12} cycloalkyl group or a $(C_{3-12}$ cycloalkyl) C_{1-3} alkyl- group each of which is optionally substituted by one or more of
 5 the following: a C_{1-6} alkyl group; fluoro, amino or hydroxy, or

R^7 represents a group $-(CH_2)_a$ phenyl in which a is 0, 1, 2, 3 or 4 and the phenyl group is optionally substituted by one or more groups represented by Z which may be the same or different or

10

R^7 represents a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more of the of the following : oxygen, sulphur or nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, C_{1-3} acyl groups, hydroxy, amino or benzyl; or

15

R^3 and R^4 independently represent a group of formula $-(CH_2)_o-O-(CH_2)_p-R^8$ in which o and p independently represent an integer 0, 1, 2, 3 or 4 and R^8 represents a C_{1-12} alkyl group or R^8 represents phenyl optionally independently substituted by one or more Z groups or R^8 represents an aromatic heterocyclic group or a saturated or partially unsaturated 5 to 8
 20 membered heterocyclic group containing one or more of one following : oxygen, sulphur or nitrogen wherein each of these rings is optionally substituted by one or more groups represented by Z which may be the same or different ;

R^3 and R^4 independently represent a C_{1-12} alkyl group optionally substituted by one or more
 25 fluoro, hydroxy, or amino; or

R^3 and R^4 independently represent a group of formula $-(CH_2)_qR^9$ in which q is 0, 1, 2, 3 or 4 and R^9 represents a C_{3-12} cycloalkyl group, phenyl, an aromatic heterocyclic group or a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or
 30 more of one following : oxygen, sulphur or nitrogen wherein each of these rings is optionally substituted by one or more groups represented by Z which may be the same or different ; or

R^3 and R^4 independently represent a group of formula $-(CH_2)_m-O-(CO)-R^{10}$ in which m represents an integer 0, 1, 2, 3 or 4, in which R^{10} represents a C_{1-12} alkyl group optionally substituted by one or more fluoro, hydroxy, or amino or R^{10} represents a group of formula $-(CH_2)_qR^9$ in which

5 q and R^9 is as previously described;

or

R^3 and R^4 independently represent a group of formula $CONR^{11}R^{12}$

in which

R^{11} and R^{12} independently represent a C_{1-6} alkyl group;

10 an (amino) C_{1-4} alkyl- group in which the amino is optionally substituted by one or more C_{1-3} alkyl groups;

a $(C_{3-12}$ cycloalkyl) $(CH_2)_g$ group wherein g is 0, 1, 2 or 3 wherein the cycloalkyl is optionally substituted by one or more fluoro, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxycarbonyl, trifluoromethyl, amino or trifluoromethoxy;

15 a group $-(CH_2)_r(phenyl)_s$ in which r is 0, 1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted one or more groups represented by Z ;

naphthyl;

anthracenyl;

20 a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, hydroxy, fluoro, trifluoromethyl, benzyl or an amino group $-NR^xR^y$ in which R^x and R^y independently represent H or C_{1-4} alkyl; 1-adamantylmethyl;

25 a group $-(CH_2)_t$ Het in which t is 0, 1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3} alkyl groups and Het represents an aromatic heterocyclic group optionally substituted by one, two or three groups selected from a C_{1-5} alkyl group, a C_{1-5} alkoxy group or halo;

or R^{11} represents H and R^{12} is as defined above;

30 or R^{11} and R^{12} together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups,

hydroxy, fluoro, trifluoromethyl, trifluoromethoxy, benzyl, C₁₋₆alkanoyl or an amino group - NR^xR^y in which R^x and R^y independently represent H or C₁₋₄alkyl ;

with the proviso that when one of R³ and R⁴ is a C₁₋₃alkyl group, a C₁₋₃alkoxymethyl group, trifluoromethyl, a hydroxyC₁₋₃alkyl group, C₁₋₃alkoxycarbonyl, carboxy, carbamoyl, or mono or di C₁₋₃alkylcarbamoyl then the other does not represent a group of formula CONR¹¹R¹².

It will be understood that where a substituent Z is present in more than one group that these substituents are independently selected and may be the same or different.

10

The term aromatic heterocyclic group means an aromatic 5-, 6-, or 7-membered monocyclic ring or a 9- or 10-membered bicyclic ring, with up to five ring heteroatoms selected from oxygen, nitrogen and sulfur. Suitable aromatic heterocyclic groups include, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl. Preferably furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl and more preferably pyrrolyl, thienyl, imidazolyl, oxazolyl or pyridyl.

Suitable saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur include, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-4-yl or piperazin-1-yl.

Further values of R^1 , R^2 , R^3 and R^4 in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

- 5 In a first group of compounds of formula, R^1 and R^2 are phenyl optionally substituted by one or more groups Z.

In a second group of compounds of formula I, R^1 and R^2 are both 4-chlorophenyl

In a third group of compounds of formula I, R^3 and R^4 independently represent a group of formula COOR^7 in which R^7 is a C_{4-8} alkyl group.

- 10 In a fourth group of compounds of formula I, R^3 represents a group of formula COOR^7 in which R^7 is a C_{4-8} alkyl group and R^4 represents a group of formula $-(\text{CH}_2)_o-\text{O}-(\text{CH}_2)_p-\text{R}^8$ in which o and p independently represent an integer 0, 1, 2, 3 or 4 R^8 represents phenyl optionally independently substituted by one or more Z groups.

- In a fifth group of compounds of formula I, each represent a group of formula $\text{CONR}^{11}\text{R}^{12}$
15 in which R^{11} and R^{12} are as previously defined.

In a sixth group of compounds of formula I, R^3 and R^4 independently represent a group of formula $\text{CONR}^{11}\text{R}^{12}$ in which R^{11} and R^{12} together with the nitrogen atom to which they are attached represent piperidino.

- In a seventh group of compounds of formula I, R^3 represents a group of formula COOR^7 in
20 which R^7 is a C_{4-8} alkyl group and R^4 represents a group of formula R^3 and R^4 independently represent a group of formula $-(\text{CH}_2)_m-\text{O}-(\text{CO})-\text{R}^{10}$ in which m represents an integer 0, 1, 2, 3 or 4, in which R^{10} represents a C_{1-12} alkyl group optionally substituted by one or more fluoro, hydroxy, or amino or R^{10} represents phenyl optionally substituted by one or more groups represented by Z which may be the same or different.

25

In an eighth group of compounds which is a sub group of the each of the first, second, third, fifth and sixth groups R^3 and R^4 are identical.

- ‘Pharmaceutically acceptable salt’, where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. All tautomers, where possible, are
30 included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

5

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine,
10 bromine or iodine.

Specific compounds of the invention are one or more of the following:

2,3-bis(4-chlorophenyl)-5,6-bis(piperidin-1-ylcarbonyl)pyrazine and

bis-2,3-(*tert*-butoxy)-5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylate and pharmaceutically

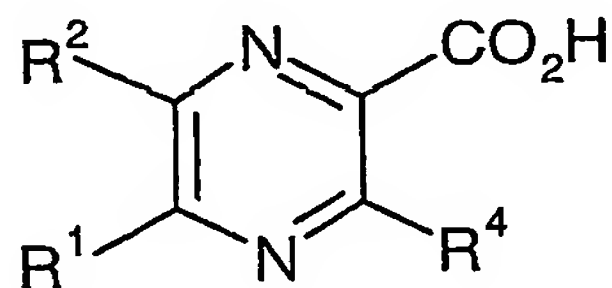
15 acceptable salts thereof.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the
20 following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

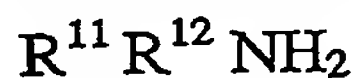
Compounds of formula I in which R^1 and R^2 are as previously defined and R^4 is a group $COOR^4$ and R^3 is $CONR^{11}R^{12}$ may be prepared by reacting a compound of formula III

25



III

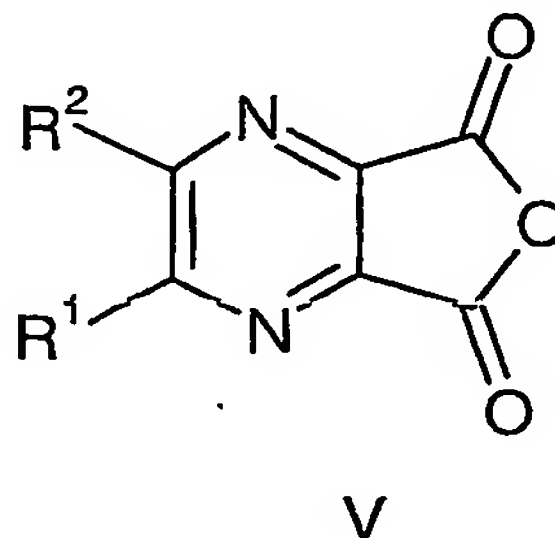
in which R^1 , R^2 and R^4 are as defined immediately previously with an amine of formula IV



IV

in which R^{11} and R^{12} are as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C .

Compounds of formula III may be prepared by reacting a compound of formula V



in which R^1 and R^2 are as previously defined with a compound of formula VI

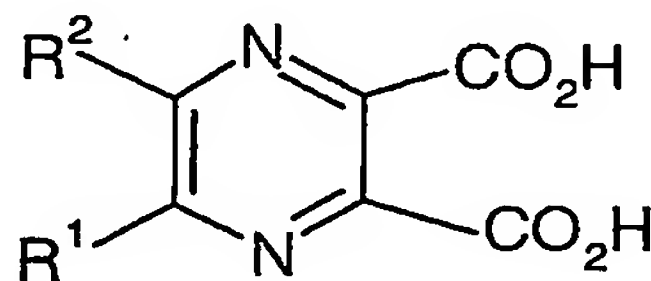


in which R^7 is as previously defined in an inert solvent, for example acetonitrile, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C .

Compounds of formula I may also be prepared by reacting a compound of formula V with a compound of formula VI and then reacting the product directly with a compound of formula IV.

Compounds of formulae III, V and VII are commercially available or may be prepared by methods known to those skilled in the art. Certain compounds of formulae II, III, IV and V are novel and are claimed as a further aspect of the present invention as useful intermediates.

Compounds of formula V may be prepared by reacting a compound of formula VIII.



VIII

in which R^1 and R^2 are as previously defined with a dehydrating agent for example acetyl chloride at a temperature in the range of 0°C to 150°C.

Other compounds of formula I may be prepared by analogous methods or by methods known
5 to those skilled in the art.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

10 Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular
15 reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

20

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal,
25 transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

30

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

5

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

10

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

30 In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders,

anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, 10
anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, 15
cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I 20
to a patient in need thereof.

The compounds of the present invention are particularly suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity 30
such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of

LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

- 5 The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).
- 10 In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates,
- 15 solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application

20 include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites,

25 whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding

30 resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor;
- a cholesterol absorption antagonist;
- a MTP (microsomal transfer protein) inhibitor ;
- a nicotinic acid derivative, including slow release and combination products;
- 10 a phytosterol compound ;
- probucol;
- an anti-coagulant;
- an omega-3 fatty acid ;
- another anti-obesity compound;
- 15 an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;
- a Melanin concentrating hormone (MCH) antagonist;
- 20 a PDK inhibitor; or
- modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;
- an SSRI;
- a serotonin antagonist;
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof,
- 25 optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount

30 of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the

other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating
5 hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt,
10 solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination
15 section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from
20 one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit
25 dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

30

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

- b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

5

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the
10 treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate
15 of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula
20 I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded
25 animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension,
30 coronary heart disease, non-alcoholic steatorrheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

ExamplesAbbreviations

DCM - dichloromethane

5 DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA - triethylamine

TFA - trifluoroacetic acid

10 DMSO-dimethyl sulfoxide

DEA - Diethylamine

PCC - Pyridinium chlorochromate

DCM - Dichloromethane

PyBOP - benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate

15 HBTU - *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium Hexafluorophosphate

DAST-(diethyl amino)sulphur trifluoride

DIEA - *N,N*-diisopropylethylamine

t triplet

s singlet

20 d doublet

q quartet

qvint quintet

m multiplet

br broad

25 bs broad singlet

dm doublet of multiplet

bt broad triplet

dd doublet of doublet

General Experimental Procedures

30 Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ¹H NMR measurements were performed on either a Varian Mercury 300 or a Varian Inova 500, operating at ¹H frequencies of 300 and 500 MHz

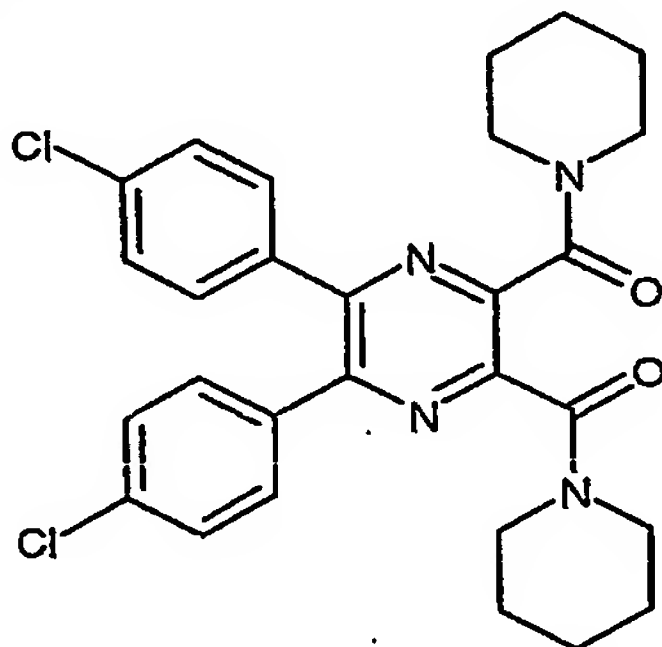
respectively. Chemical shifts are given in ppm with CDCl_3 as internal standard. CDCl_3 is used as the solvent for NMR unless otherwise stated. Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M NH_4Ac :acetonitrile 95:5).

For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

Examples of the Invention

Example 1

2,3-bis(4-chlorophenyl)-5,6-bis(piperidin-1-ylcarbonyl)pyrazine



Oxalyl chloride (1.3 ml, 15 mmol) was added to a suspension of 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid, (589 mg, 1.51 mmol) in DCM (10 ml) and DMF (0.2 ml). After 10 minutes the solvent was removed in vacuo. The residue was retaken in dry toluene, filtrated through celite, and evaporated twice in order to completely remove excess oxalyl chloride. The residue was dissolved in DCM (20 ml) and a solution of piperidine (773 mg, 9.08 mmol) in DCM was added. After 1 h the reaction mixture was washed with hydrochloric acid (2 M), water and dried (magnesium sulfate). Evaporation of the solvent gave the target compound (43mg, 54%).

^1H NMR (400 MHz) δ 7.40 (d, 4H), 7.30 (d, 4H), 3.74-3.69 (m, 4H), 3.49-3.43 (m, 4H), 1.72-1.64 (m, 12H).

MS m/z calcd for $[\text{C}_{28}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2]\text{H}^+$ 523.1668, found 523.1655 ($\text{M}+\text{H}$) $^+$.

Example 2

Bis-2,3-(*tert*-butoxy)-5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylate may be prepared by reacting 3-(*tert*-butoxycarbonyl)-5,6-bis(4-chlorophenyl)pyrazine-2-carboxylic acid with *tert*-butanol by methods known to those skilled in the art.

Preparation of Intermediatesa) 1,2-bis(4-chlorophenyl)-2-hydroxyethanone

10 To 4-chlorobenzaldehyde (140.6 g, 1 mol) in ethanol (130 ml) was added a solution of sodium cyanide (10.6 g, 0.216 mol) in water (105 ml). The mixture was heated at reflux for 2.5 h and then extracted with DCM. The organic phase was washed with sodium bisulfite solution and the solvent was evaporated in vacuo. The compound was isolated by crystallization from diethyl ether/heptane. 48 g, 34%.

15 ^1H NMR (400 MHz) δ 7.82 (d, 2H), 7.38 (d, 2H), 7.30 (d, 2H), 7.24 (d, 2H), 5.87 (s, 1H), 4.47 (s, 1H).

MS m/z 279, 281 (M-H) $^-$.

b) 1,2-bis(4-chlorophenyl)ethane-1,2-dione

20 1,2-bis(4-chlorophenyl)-2-hydroxyethanone, (90 g, 0.320 mol) and nitric acid (170 ml) were heated at 100°C until the evolution of nitrogen oxides ceased after 4 hours. The reaction mixture was cooled, and water (250 ml) was carefully added. The crude product was filtered, washed several times with water and dried under reduced pressure to give a yellow solid (40.4 g, 45%).

25 ^1H NMR (500 MHz) δ 7.94 (d, 4H), 7.53 (d, 4H).

c) 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile

1,2-bis(4-chlorophenyl)ethane-1,2-dione, (20 g, 71.65 mmol), diaminomaleonitrile (8.5 g, 78.82 mmol) and acetic acid (6 ml) in ethanol (140 ml) and water (93 ml) were heated at 75 °C overnight. The reaction mixture was cooled, and water was added. The precipitate was filtered and washed with ethanol and then ether. The crude product was dissolved in DCM and treated with activated charcoal, then filtered through celite. After evaporation, a solid was formed and recrystallized from DCM/ethanol to give a pale yellow solid (17.3 g, 69%).

¹H NMR (400 MHz) δ 7.49 (d, 4H), 7.38 (d, 4H).

10 d) 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid

To 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile, (16.3 g, 46.28 mmol) and KOH (26 g, 463 mmol) in water (84 ml) was added hydrogen peroxide (35%, 19 ml) followed by a few drops of nonanol to reduce foaming. The reaction mixture was heated at reflux for 2h, cooled and washed once with diethyl ether and acidified to pH 4 with 2M HCl. The precipitate was collected through a filter, washed with water and dried under reduced pressure to give the crude product. The crude product was converted to dimethyl ester by refluxing with hydrogen chloride/methanol (100 ml) and purified by HPLC, giving 12.85 g of the methyl ester. The resulting methyl ester was treated with lithium hydroxide (2.95 g, 0.123 mmol) in acetonitrile (140 ml) and water (90 ml) at ambient temperature for 1.5 h. The acetonitrile was removed under reduced pressure and the aqueous solution was washed once with diethyl ether. Acidification with hydrochloric acid (2M) and filtration gave the title compound (11.8 g, 66% mmol) as a pale yellow solid.

¹H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H). MS *m/z* 389, 391 (M+H)⁺.

25 e) 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione

5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid (6.7 g, 17.30 mmol) and acetyl chloride (20 ml) were heated at reflux overnight. The acetyl chloride was removed under reduced pressure to give the title compound (6.2 g, 97%) as a pale yellow solid.

¹H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H).

30

f) 3-(*tert*-butoxycarbonyl)-5,6-bis(4-chlorophenyl)pyrazine-2-carboxylic acid

To a solution of 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione, (877 mg, 2.36 mmol) in acetonitrile (15ml) were added *tert*-butanol (876 mg, 11.8 mmol) and DMAP (346 mg, 2.8

mmol). After 30 minutes the solvent was removed in vacuo and the residue was dissolved in DCM. Washed with 2 M potassium hydrogen sulfate and water followed by drying (magnesium sulfate), filtration and evaporation of the solvent gave a residue which was purified by HPLC to give the title compound (431 mg, 41%).

5 ^1H NMR (400 MHz) δ 7.35-7.17 (m, 8H), 1.57 (s, 9H)

MS m/z 445 ($\text{M}+\text{H}$) $^+$, 443 ($\text{M}-\text{H}$) $^-$.

Pharmacological Activity

10 Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al, Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

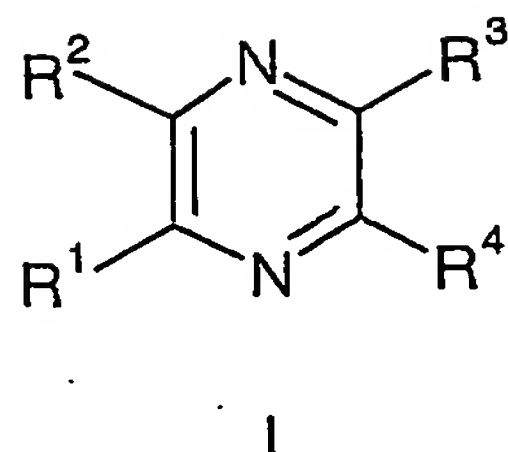
15 10 μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200 μl of 100mM NaCl, 5mM MgCl_2 , 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100 μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1 μCi [^{35}S]-GTP γS . The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using
20 a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM MgCl_2 , 50mM NaCl). Filters were then covered with scintillant and counted for the amount of [^{35}S]-GTP γS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and
25 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation $y=A+((B-A)/(1+((C/x)^D)))$ and the IC50 value determined as the concentration required to give half maximal inhibition of GTP γS binding under the conditions used.

30 The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

Claims:

1. A compound of formula (I)



5 and pharmaceutically acceptable salts thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is independently optionally substituted by one or more groups represented by Z;

Z represents a C_{1-8} alkyl group, a C_{1-6} alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, mono or di C_{1-3} alkylamido, C_{1-3} alkylsulphonyl, C_{1-3} alkylsulphonyloxy, C_{1-3} alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3} alkyl carbamoyl, sulphamoyl, acetyl, an aromatic heterocyclic group which is optionally substituted by one or more halo, C_{1-4} alkyl, trifluoromethyl or trifluoromethoxy and a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, hydroxy, fluoro, benzyl or an amino group $-NR^xR^y$ in which R^x and R^y independently represent H or C_{1-4} alkyl;

R^3 and R^4 independently represent a group of formula $(CH_2)_nCOOR^7$

20

in which n is 0, 1, 2, 3 or 4; and R^7 represents a C_{1-12} alkyl group, a C_{3-12} cycloalkyl group or a $(C_{3-12}$ cycloalkyl) C_{1-3} alkyl- group each of which is optionally substituted by one or more of the following: a C_{1-6} alkyl group; fluoro, amino or hydroxy, or

25 R^7 represents a group $-(CH_2)_a$ phenyl in which a is 0, 1, 2, 3 or 4 and the phenyl group is optionally substituted by one or more groups represented by Z which may be the same or different or

R^7 represents a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more of the of the following : oxygen, sulphur or nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, C_{1-3} acyl groups, hydroxy, amino or benzyl; or

5

R^3 and R^4 independently represent a group of formula $-(CH_2)_o-O-(CH_2)_p-R^8$ in which o and p independently represent an integer 0, 1, 2, 3 or 4 and R^8 represents a C_{1-12} alkyl group or R^8 represents phenyl optionally independently substituted by one or more Z groups or R^8 represents an aromatic heterocyclic group or a saturated or partially unsaturated 5 to 8

10 membered heterocyclic group containing one or more of one following : oxygen, sulphur or nitrogen wherein each of these rings is optionally substituted by one or more groups represented by Z which may be the same or different ;

R^3 and R^4 independently represent a C_{1-12} alkyl group optionally substituted by one or more
15 fluoro, hydroxy, or amino; or

R^3 and R^4 independently represent a group of formula $-(CH_2)_qR^9$ in which q is 0, 1, 2, 3 or 4 and R^9 represents a C_{3-12} cycloalkyl group, phenyl, an aromatic heterocyclic group or a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or
20 more of one following : oxygen, sulphur or nitrogen wherein each of these rings is optionally substituted by one or more groups represented by Z which may be the same or different ; or

R^3 and R^4 independently represent a group of formula $-(CH_2)_m-O-(CO)-R^{10}$ in which m
25 represents an integer 0, 1, 2, 3 or 4 , in which R^{10} represents a C_{1-12} alkyl group optionally substituted by one or more fluoro, hydroxy, or amino or R^{10} represents a group of formula -
 $(CH_2)_qR^9$ in which
q and R^9 is as previously described;

or

30 R^3 and R^4 independently represent a group of formula $CONR^{11}R^{12}$
in which

R^{11} and R^{12} independently represent a C_{1-6} alkyl group;

an (amino) C_{1-4} alkyl- group in which the amino is optionally substituted by one or more C_{1-3} alkyl groups;

a $(C_{3-12}\text{cycloalkyl})(CH_2)_g$ group wherein g is 0, 1, 2 or 3 wherein the cycloalkyl is optionally substituted by one or more fluoro, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxycarbonyl,

5 trifluoromethyl, amino or trifluoromethoxy;

a group $-(CH_2)_r(\text{phenyl})_s$ in which r is 0, 1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2

and the phenyl groups are optionally independently substituted one or more groups

represented by Z;

naphthyl;

10 anthracenyl;

a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups, hydroxy, fluoro, trifluoromethyl, benzyl or an amino group $-NR^xR^y$ in which R^x and R^y independently represent H or C_{1-4} alkyl ;

15 1-adamantylmethyl;

a group $-(CH_2)_t\text{Het}$ in which t is 0, 1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3} alkyl groups and Het represents an aromatic heterocyclic group optionally substituted by one, two or three groups selected from a C_{1-5} alkyl group, a C_{1-5} alkoxy group or halo ;

20 or R^{11} represents H and R^{12} is as defined above;

or R^{11} and R^{12} together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen;

wherein the heterocyclic group is optionally substituted by one or more C_{1-3} alkyl groups,

25 hydroxy, fluoro, trifluoromethyl, trifluoromethoxy, benzyl, C_{1-6} alkanoyl or an amino group $-NR^xR^y$ in which R^x and R^y independently represent H or C_{1-4} alkyl ;

with the proviso that when one of R^3 and R^4 is a C_{1-3} alkyl group, a C_{1-3} alkoxymethyl group, trifluoromethyl, a hydroxy C_{1-3} alkyl group, C_{1-3} alkoxycarbonyl, carboxy, carbamoyl, or mono

30 or di C_{1-3} alkylcarbamoyl then the other does not represent a group of formula $CONR^{11}R^{12}$.

2. A compound selected from one or more of the following:

2,3-bis(4-chlorophenyl)-5,6-bis(piperidin-1-ylcarbonyl)pyrazine and

bis-2,3-(*tert*-butoxy)-5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylate and pharmaceutically acceptable salts thereof.

3. A compound of formula I as claimed in any previous claim for use as a medicament.

4. A pharmaceutical formulation comprising a compound of formula I, as defined in any either claim 1 or claim 2 and a pharmaceutically acceptable adjuvant, diluent or carrier.

5. Use of a compound of formula I according to claim 1 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

6. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound of formula I according to claim 1 to a patient in need thereof.

7. A compound as defined in either claim 1 or claim 2 for use in the treatment of obesity.

ABSTRACT

5

Title : Therapeutic Agents

10

The present invention relates to compounds of formula I and processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

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